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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	15

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/332,522	COSTA ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04-06-01* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-11,13-18,22,23,25-28 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-11,13-18,22,23,25-28 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. Amendment filed 4-06-01 has been entered.

2. Claims 5, 7, 12, 19-21, 24, and 29-33 have been canceled.

3. Claim 1-4, 6, 8-11, 13-18, 22-23, 25-28, and 34-36 are pending.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6, 8-11, 13-18, and 34-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claims 1, 2 and newly presented claims 34-36 recite a C.elegans that has been genetically engineered, however, the specification as originally filed does not disclose a C.elegans that has been genetically engineered. Applicants have noted that the amendment is supported by specification on page 5, lines 26-27 and lines 31-33, page 20 lines 14-17, page 21 line 1 and page 29 line 28-30. However, none of these sections disclose a C.elegans that has been genetically engineered. It is noted that page 20, lines 14-17 discloses genetically modified animal models (in vivo models) such as C.elegans while the term "genetically engineered" is used for cell lines (in vitro). Accordingly, the term " A C.elegans that has been genetically engineered" is considered a new matter.

Amended claims 1, 11, 13, and 15 recite the term "intestinal defect phenotype", however the specification as originally filed does not disclose this term. Applicants have noted that the amendment is supported by specification on page 5, lines 26-27 and lines 31-33, page 20 lines 14-17, page 21 line 1 and page 29 line 28-30. However, none of these sections disclose the term "intestinal defect

phenotype". Accordingly, the term "intestinal defect phenotype" is considered a new matter.

6. Claims 1-4 and 6-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic C.elegans, wherein the nucleic acid sequence of ceSREBP is disclosed in SEQ ID NO 1 and the amino acid sequence of said ceSREBP is disclosed in SEQ ID NO 2, wherein the endogenous ceSREBP gene of the said transgenic C.elegans has been mutated by transposon insertion mutagenesis, wherein said mutation results in a phenotype of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles, and uses of said transgenic C.elegans, does not reasonably provide enablement for any and all nematodes that have genetically modified expression or miss-expression of any and all SREBP proteins and uses of any and all such genetically modified C.elegans for reasons of record set forth in the previous office action of 10-6-2000. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 4-6-01 have been fully considered but they are not persuasive. Applicants have argued that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the claimed genetically engineered C.elegans and have cited pages 5 and 16 of the specification. However, these sections of the specification do not address the issues raised in the previous office action. For example, it was noted in the previous office action that the specification does not provide any disclosure as to what is the function of the ceSREBP. In response, Applicants have cited a review article by Chitwood et al that C.elegans does not synthesize sterols de novo and therefore, ceSREBP will function in fatty acid metabolism. However, these arguments are merely speculative at the best because Chitwood et al also teach that C.elegans could synthesize cholesterol from sitosterol which would indicate that they do have

sterol metabolism pathway (see figure 1). Since the C.elegans in the instant case were not maintained in a sterol free medium, accumulation of lipid droplets could have resulted due to alteration in sterol metabolism. In other words Applicants' arguments that ceSREBP, SCAP, and S2P function in fatty acid metabolism are not persuasive. Regarding the issue of which enzyme of cholesterol or fatty acid metabolism ceSREBP regulates, Applicants have argued that the genome sequence of C.elegans does not have the sequence for any other C.elegans SREBP genes and have cited a review article of Genome Sequence of C.elegans published in Science 1998. It is noted that the cited article does not teach whether a SREBP gene or multiple SREPB genes are present in C.elegans and the Applicants have not directed to the section in the article where the statement that only one SREBP is present in C.elegans is made. Applicants have used an example of IGF-I to make a point that ceSREBP may be doing the functions of multiple forms of mammalian SREBP or human SREBP. Again the comparison is not correct because IGF-I is a receptor, whereas SFEBP is a transcription factor. For a transcription factor to be regulating the function of multiple genes, it would have to have response element/domain for all regulated genes or all the gene would have to be regulated by the same mechanism and the specification does not teach whether SREBP can regulate the function of all the genes of fatty acid metabolism that are regulated by the mammalian counter part.

The next enablement issue is: whether all the methods of creating genetic modification would have produced transgenic nematodes or C.elegans with same phenotype and whether the changes produced would have been inheritable. Applicants have argued "claim 1 does not require that the intestinal defect phenotype be inheritable and progeny that inherit the intestinal defect phenotype are encompassed by the claim but progeny that inherit the intestinal defect phenotype are not encompassed by the claim". Applicants have further argued that such features are not needed for the genetically engineered worms to have utility. Again these arguments are not persuasive because if the mutation or changes in the C.elegans are not incorporated in the genomic DNA, how can the phenotype be inheritable and inheritable phenotype can only be produced if the changes are in

the genomic DNA. Applicants' arguments that the number of generations for transmittal of RNA interference phenotype may not be relevant is not persuasive because it would be relevant for inheritable phenotype and to reproduce progeny of the C.elegans with the same phenotype. If the phenotype was not inheritable progeny after progeny, the change in the genome has to be carried out every time an artisan needed a C.elegans of the claimed invention and each time a new C.elegans would be created whose phenotype would not be the same as the previous worm or another worm.

Applicants have argued that uniformity is not legally required, again this argument is not persuasive because if the phenotype was not uniform, the C.elegans prepared by one method would not be same as the other one since the claim is to a genetically engineered C.elegans with a particular phenotype. It is reiterated that RNA interference method would be rather a transient expression method and may not produce transgenic nematodes. Regarding the method of chemical mutagenesis, it is noted that the specification has provided a review of methods of mutagenesis, however, no working examples have been disclosed. While the enablement of the method of chemical mutagenesis is not an issue, the issue is whether the mutant C.elegans would have same phenotype. Regarding the issue of phenotype, applicants have argued that 25% of the heterozygous C.elegans showing the phenotype is in agreement with normal Mendalian segregation. However, as noted above, if the transmission is not germ line transmission, how can one produce C.elegans with the same phenotype again and again every time the assay is repeated. It is noted that Applicants have provide a declaration that even by chemical mutagenesis they were able to generate a C.elegans that had a pale intestine phenotype, however, it is not clear whether SCAP or S2P mutants would also be produced because the method is not a targeted disruption in a particular gene, rather it is a random mutagenesis.

Regarding the issue that the specification is not enabling for a C.elegans expressing SREBP protein, Applicants have cited the reference of Sakai et al that teaches the expression of truncated forms of SREBP-2 and SCAP and that example 4 shows the over expression of a dominant negative form of SREBP in C.elegans, it

is noted that these are truncated forms of SREBP, not the full length protein and the effect of the over expressing a full length SREBP protein on the physiology of the animal will not be the same and could not be predicated based on the teachings of the prior art or the specification. Applicants have argued that specification provides the sequence of SREBP whereas the information of SCAP and S2P is present in the database and using this information an artisan could practice the invention. However, these arguments are not persuasive because it is not clear whether the sequence which the Applicants have designated as SCAP or S2P due to sequence similarities have the function of their mammalian counterparts because the specification does not teach as to what type of homology is there and there is nothing in the prior art to suggest whether these sequences of SCAP or S2P in the database are full length or what type of protein is encoded by these sequences and how are the proteins related and the specification has not provided any of these teachings. It is reiterated that even for SREBP, it is not clear how an artisan would have used such C.elegans because the specification does not teach what would have been the phenotype of such animals or if the animals would have been viable at all because the specification has not disclosed or taught what is the precise function of the SREBP. Furthermore, as noted in the previous office action, the phenotype due to the mutation in the gene which may have resulted in the loss of SREBP, SCAP or S2P protein could not indicate that over expression would have the same effect on the animals. It is possible that block in the function of the protein may have affected another member of the pathway in addition to the function of SREBP, SCAP or S2P, whereas when it is over expressed it may be affecting the activity of a different protein which may also be important for another pathway. Therefore, results obtained by inhibiting the function of a gene can not be correlated with the results obtained when same gene is being over expressed. Regarding, the use of different promoters for expressing the protein, it is noted that one would not know that when the SREBP protein is expressed in gonadal cells, its effects would be the same as when it is expressed in the intestine or in any other organ. Again an artisan would not have known whether expression of the SREBP protein in different tissues or at different stages of development would have

produced animals with same phenotype or what phenotype and without this information, an artisan would not have been able to distinguish all thee animals and would not have known how to use them.

Applicants have noted that the rejection of claim 6 was not clear. In response it is noted that claim 6 was interpreted to encompass a reporter expression vector in which SREBP regulatory sequence controls the expression of a reporter gene. Accordingly, it was noted that the claimed invention is not enabled because while a marker gene can demonstrate the expression pattern of a gene in an animal, it can not provide any clue as to what would be the effect of the gene product on the physiology of the animal or what phenotypes would be produced if the gene product is over expressed in an animal. Regarding claims 11, 16, and 17, it is reiterated that the specification does not teach or provide any evidence whether both over expression as well as inhibition of ceSREBP or SCAP or S2P would result in pale intestine and Applicants arguments do not address this issue. Furthermore, a truncated SREBP-2 in CHO cells, due to recombinations in the intron that terminates at codon 460, results in sterol resistant phenotype in these cells, however, no such event in SREBP has been observed (see last paragraph in column one on page 335). This would indicate that different SREBPs (SEBP, SCAP, and S2P) may undergo different processing and metabolism and therefore, phenotype due to their mutation or over expression might vary. The specification as filed does not provide any guidance whether the same phenotype will be produced when the expression of SREBPs (SEBP, SCAP, S2P) in C.elegans was altered (over expressed or inhibited or mutated). Therefore, an artisan would not have known whether a fluorescently labelled fatty acid conjugate would have been able to measure the lipid content in all the C.elegans encompassed by the claimed invention.

The 1.132 declaration of Cynthia Seidel-Dugan has been considered and discussed above appropriately.

In conclusion, an artisan would not have been able to make and use the claimed invention commensurate in scope of the claims because the specification does not provide sufficient guidance and working examples for an artisan to practice the invention without undue experimentation and therefore, limiting the

scope of the claimed invention to a transgenic C.elegans, wherein the nucleic acid sequence of ceSREBP is disclosed in SEQ ID NO 1 and the amino acid sequence of said ceSREBP is disclosed in SEQ ID NO 2, wherein the endogenous ceSREBP gene of the said transgenic C.elegans has been mutated by transposon insertion mutagenesis, wherein said mutation results in a phenotype of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles, and uses of said transgenic C.elegans is proper.

7. Claims 1-4, 6-11, and 34-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 10-6-00.

Response to Arguments

Applicant's arguments filed 4-6-01 have been fully considered but they are not persuasive. Applicants have argued that after amending claim 1, the specification provides sufficient written description of their invention. However, these arguments are not persuasive because claimed invention encompass genetically engineered C.elegans which over express full length or fragments of SREBPs (SREBP, SCAP or S2P) or wherein the expression of SREBPs (SREBP, SCAP or S2P) has been interrupted, the phenotypes and characteristics of all the C.elegans may not be known and one would not know whether same phenotype would have been produced in all the C.elegans encompassed by the claimed invention. Furthermore, it is not clear what would have been the result of the ablation of SREBPs (SREBP, SCAP or S2P) or expression in different tissues would have been, the normal function of which is not well established in C.elegans in all the C.elegans encompassed by the invention.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of

the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

8. Claim 22, 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide molecule that comprises the sequence of SEQ ID NO 1 and encodes the amino acid sequence of SEQ ID NO 2, a process of producing C.elegans SREBP wherein said C.elegans SREBP consists of the amino acid sequence disclosed in SEQ ID NO 2 by a culturing a host cell that comprises a vector wherein said vector comprises the nucleic acid sequence of SEQ ID NO 1, does not reasonably provide enablement any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is not enabling for all the polynucleotides and host cells and method encompassed by the claimed invention because the specification only teaches a polynucleotide that encodes the polypeptide of SEQ ID NO 2. The issue is: would all the polynucleotides as disclosed claim 22 have the biological activity of SREBP or would produced a phenotype in C.elegans when expressed in C.elegans. It is noted that the claimed polynucleotides would encompass those in which at least 20% nucleotides are different from the sequence of SEQ ID NO 1 in the region of nt 1-3419 which would mean a change of 680 nt in the region. Likewise claimed polynucleotides would also encompass those that encode a protein that have at least 20% amino acid difference compared to SEQ ID NO 2 in the region of aa 1-1113, which would mean a change of at least 220 amino acids. And such changes when evenly spread over the entire protein would alter the activity of the protein. Likewise a protein encoded by the nucleotides sequence claimed in SEQ ID NO 1 would mean changing every other amino acid if changes were made in the third base of the codon or if the changes were made in non-wobble positions. Again the resultant protein would not retain the function of the protein disclosed in SEQ ID

NO 2. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the nucleotide sequence of SEQ ID NO 1 would encode a amino acid sequences that would retain the biological activity of the SREBP. The specification does not teach how to use a nucleic acid that would have encoded a protein which was derived from the protein of SEQ ID NO 2 but did not have the function of the starting protein. Alternatively, the specification does not teach how would an artisan have made a polynucleotide that would have encoded a protein in which every other amino acids would have been changed but the protein would have retained the function of the starting protein. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Even if these polynucleotides were to be used as a probe and the 20% change in the nucleotide sequence was to be spread across the entire length of the polynucleotide, they will not be able to specifically recognize a related polynucleotide or the polynucleotide of SEQ ID NO 1. If one used degenerate

nucleotides for every amino acid in the protein, resultant polypeptide would not hybridize to a sequence of SEQ ID NO 1.

In summary, the specification is not enabling for the claimed polynucleotides, host cells and vectors commensurate with the scope of the claims and therefore, limiting the scope of the claimed invention to an isolated polynucleotide molecule that comprises the sequence of SEQ ID NO 1 and encodes the amino acid sequence of SEQ ID NO 2, a process of producing C.elegans SREBP wherein said C.elegans SREBP consists of the amino acid sequence disclosed in SEQ ID NO 2 by a culturing a host cell that comprises a vector wherein said vector comprises the nucleic acid sequence of SEQ ID NO 1 is proper.

Response to Arguments

Applicant's arguments with respect to claims 22, 26-28 have been considered but are moot in view of the new ground(s) of rejection due to the amendment to these claims.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-4, 6, 8-11, 13-18, and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 13, and 15 are vague and indefinite because they recite the term the term "an intestinal defect phenotype" and the specification does not define the term.

Claim 13 is vague and indefinite because there is no nexus between the preamble of the claim and the steps of the claim because the last step of the claim recites identification of a gene of interest that is capable of modifying the function of a SREBP pathway protein, while the preamble recites a method of identifying lipid metabolism.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.